UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

NOVARTIS VACCINES AND DIAGNOSTICS, INC., NOVARTIS PHARMA AG, and GRIFOLS WORLDWIDE OPERATIONS LIMITED, Plaintiffs, -v- REGENERON PHARMACEUTICALS, INC., Defendant.	18cv2434(DLC) OPINION AND ORDER

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DENISE COTE, District Judge:

This Opinion addresses the second claim construction dispute in this action. Novartis Vaccines and Diagnostics, Inc., Novartis Pharma AG, and Grifols Worldwide Operations Limited (together, "Novartis") have sued Regeneron Pharmaceuticals, Inc. ("Regeneron") for infringement of United States Patent No. 5,688,688 (the "'688 Patent") entitled "Vector for Expression of a Polypeptide in a Mammalian Cell." The '688 Patent contains 24 claims and describes a biotechnology tool that allows researchers to modify cells to produce a desired protein by delivering foreign DNA into host cells.

On March 20, 2019, this Court construed five sets of terms found in the '688 Patent's claims. See Novartis Vaccines & Diagnostics, Inc. v. Regeneron Pharm., Inc., No. 18cv2434(DLC), 2019 WL 1274790 (S.D.N.Y. Mar. 20, 2019) (the "March 20 Opinion"). Familiarity with the March 20 Opinion is presumed. Shortly thereafter, the parties stipulated to a judgment of non-infringement as to all but one claim -- Claim 17 -- in the '688 Patent. The parties now disagree as to the meaning of three terms in the remaining claim. The three terms were not construed in the March 20 Opinion. Pursuant to Markman v. Westview Instruments, Inc., 517 U.S. 370 (1996), this Opinion

adopts Regeneron's constructions for two of the three disputed terms and. A hearing will be scheduled to assist in construction of the third term.

Background

The '688 Patent describes a bioengineering process for introducing foreign DNA into a host cell. The basic principles of molecular biology and genetic engineering that form the basis of the technology were summarized in the March 20 Opinion and, for the most part, are not repeated here. Certain principles that are particularly relevant to the three disputed terms are re-described and elaborated upon below.

Biotechnology Principles

For purposes of this Opinion, the terms "polypeptide" and "protein" are interchangeable. A polypeptide is a chain of amino acids linked by peptide bonds. A sequence of three nucleotides (the building blocks of DNA) make up a codon, which codes for a specific amino acid. There are 20 different amino acids that can be arranged in different sequences in order to make a unique polypeptide. Polypeptides, or proteins, perform a wide range of cellular tasks and biotechnology companies use proteins to detect disease and for therapeutic purposes.

Polypeptides are created and expressed through processes known as "transcription" and "translation." DNA within a cell's

nucleus is transcribed or copied onto a template, known as ribonucleic acid ("RNA") or messenger RNA ("mRNA"), which then leaves the cell's nucleus, where it is translated or read by cellular machinery to produce a protein.

Regulatory DNA sequences send signals that initiate and affect transcription. A "promoter" region of DNA is a segment of DNA that signals where transcription starts. A "transcription initiation site" is the particular nucleotide where transcription begins. The promoter region is found near the front of the transcription initiation site and, diagrammatically, is to the left (or "upstream" or the "5'" direction) of the DNA sequence that is to be transcribed. An "enhancer" is a regulatory DNA sequence that influences the rate at which DNA is transcribed. Enhancers may be found upstream (5') or downstream (3') of the transcription initiation site and may be found either near or thousands of base pairs away from the promoter. While promoters are necessary in order for transcription to occur, enhancers are not.

Vectors, DNA molecules that deliver foreign DNA into a host cell, can contain regulatory DNA sequences. These sequences send signals that can affect cell processes, such as the regulation of transcription or translation. The regulatory sequences added to a vector are often taken from viruses that infect mammals. Scientists are able to insert promoter,

enhancer, and intron sequences from a mammalian virus into a vector.[1] One mammalian virus source of regulatory DNA is the human cytomegalovirus ("HCMV").

Heterologous means from a different organism. In the context of a vector, it is understood to indicate DNA from a different organism than the organism from which other DNA in the vector originates.

Scientists use plasmids, a type of vector, to produce (or express) proteins in a host cell.[2] Scientists have used plasmids to effect expression of man-made or "fusion" proteins. For example, scientists can chemically synthesize human insulin, a protein naturally produced in the human body, by synthesizing DNA coding for the two protein chains that together form insulin, inserting that DNA into a plasmid, and inserting that plasmid into bacterial cells.

The two Regeneron products at issue in this lawsuit, Eylea and Zaltrap, both use a protein called aflibercept produced through a stable expression system in a Chinese Hamster Ovary

[1] An intron is a DNA sequence that does not code for proteins. It may include regulatory DNA sequences.

[2] For a more detailed discussion of the use of vectors to produce proteins, see March 20 Opinion, 2019 WL 1274790, at *2.

("CHO") cell line.[3] Aflibercept is a fusion protein that was engineered from portions of three different human proteins. Aflibercept is not a protein that is found in nature.

The '688 Patent

The '688 Patent is entitled "Vector for Expression of a Polypeptide in a Mammalian Cell." The '688 Patent contained 24 claims and was filed on August 10, 1994 and issued on November 18, 1997. The '688 Patent was filed in a chain of applications that descended from a patent filed on December 24, 1987 and issued on October 20, 1992 ("the '949 Patent"). The specifications for the '949 Patent and the '688 Patent are identical.

The specification emphasizes the use of the claimed invention in the production of Human Immunodeficiency Virus ("HIV") proteins that would be useful in efforts to diagnose and treat HIV. Although, as described below, the patent's claims underwent significant amendment beginning in 1995, the specification has never been amended and indeed pre-dates the '688 Patent. As a result, it is particularly challenging to locate passages in the specification that illuminate the meaning of the claims.

[3] For a more detailed discussion of cell lines used for expression of proteins, see March 20 Opinion, 2019 WL 1274790, at *3.

Example 2.3.2

Example 2.3.2 of the specification, titled "Expression of gp120env using CMV IE-1 promoter," is the only example in the specification that discloses the patent's claims as they are presently constituted. It describes the insertion of a region of DNA that codes for an HIV protein -- the gp120 polypeptide -- into a mammalian cell expression vector, called plasmid pCMV6a, in order to effect expression of the gp120 polypeptide at an increased rate. With several terms relevant to the discussion below emphasized, plasmid pCMV6a is described in Example 2.3.2 as

> a mammalian cell expression vector which contains the transcriptional regulatory region from human cytomegalovirus immediate early region, HCMV IE1. The plasmid contains the SV40 polyadenylation region derived from pSV7d . . . ; the SV40 origin of replication . . . ; and the HCMV IE1 promoter as a 1.7 kbp SspI-SalI fragment. . . . The HCMV IE1 promoter region contains the region encoding the first exon (5' untranslated), the first intron and the start of the second exon. . . .

(Emphasis supplied.)

The pCMV6a plasmid is depicted in Figure 29 of the specification.

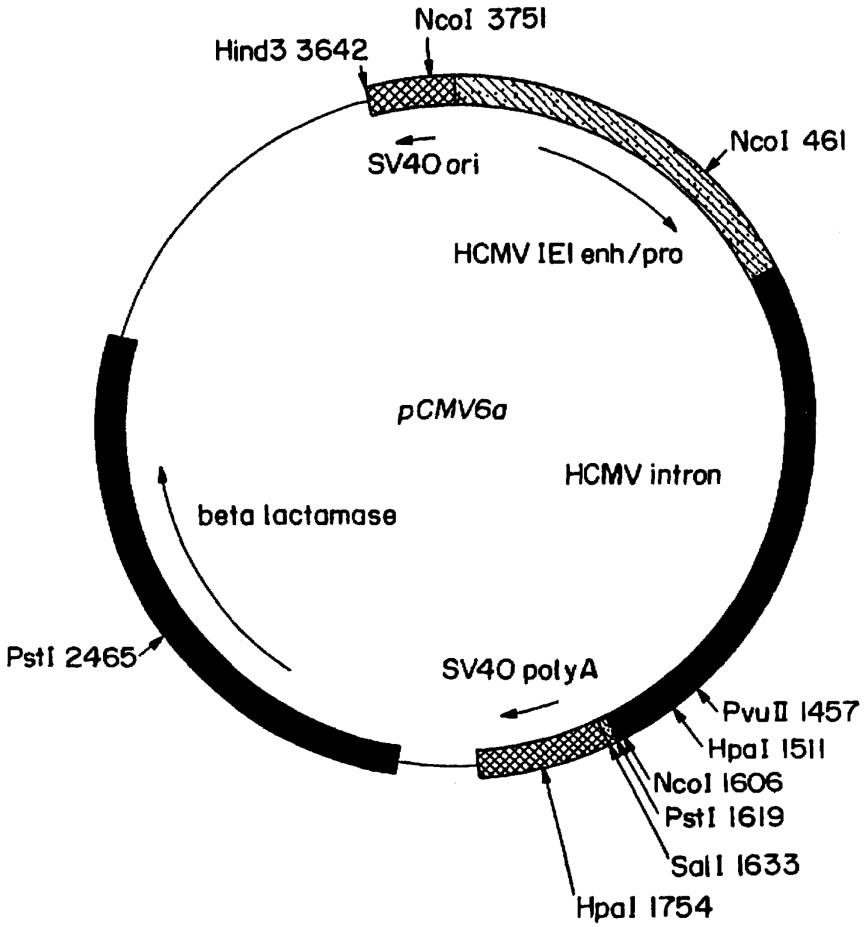

FIG. 29

Specification References to Fusion

As described below, Novartis attempts to find support in other passages in the specification for its proposed construction of Claim 17. These passages refer to fused proteins or the process of fusion and some are described here.

In the specification's "Summary of the Invention" section, the first paragraph states:

> Nucleotide sequences and expression of nucleotide sequences are provided for detecting the presence of complementary sequences associated with [HIV] . . . and for producing polypeptides. . . . The double-stranded sequences may find use as genes coding for expression of polypeptides, either fragments or complete polypeptides expressed by the virus or fused proteins, for use in diagnosis of HIV infection or evaluating stage of infection, the production of antibodies to HIV, and the production of vaccines. . . .

(Emphasis supplied.)

In the section of the specification titled "Modes for Carrying out the Invention," one paragraph reads as follows:

> The double-stranded DNA sequences, either isolated and cloned from proviral DNA or cDNA or synthesized, may be used for expression of polypeptides which may be a precursor protein subject to further manipulation by cleavage, or a complete mature protein or fragment thereof. . . . The sequence may code for any greater portion of or the complete polypeptide, or may include flanking regions of a precursor polypeptide, so as to include portions of sequences or entire sequences coding for two or more different mature polypeptides. . . .

(Emphasis supplied.) The paragraph that precedes this paragraph describes employing fragments of gag or env genes (both mammalian virus polypeptides) to screen HIV infected cells. The paragraph that follows describes a process to be used in splicing nucleotide sequences.

In the same "Modes for Carrying out the Invention" section, another paragraph explains:

> In many cases it will be desirable to express the recombinant HIV polypeptide as a fusion protein. . . . The fusion proteins approach allows the addition of a signal sequence to the HIV polypeptide so that the product is secreted by the expression host. . . . In one embodiment . . . two HIV sequences from different immunogenic domains of the virus, such as gag and env, are fused together. This produces a single fusion protein with the immunogenic potential of the two parent polypeptides.

(Emphasis supplied.)

Several examples in the specification also describe fusion during their discussion of expression systems. Example 2.2.2 of the specification is titled "Expression of tPA/gp160." The example describes the creation of an expression system that will express a fusion of human tissue plasminogen activator ("tPA") and gp160 (an HIV polypeptide). The example describes excising the "signal sequence from tPA," which is then "fused to the 5' end of gp160." Example 2.3.1, titled "Expression of engineered gp120 in pS7Vd," describes a "fragment containing . . . signal sequences from human tPA fused to the 5' end of the env." Neither example 2.2.2 nor example 2.3.1 describe a plasmid with HCMV components.

Example 2.5 of the specification is titled "Expression of gag-env fusion protein." This example describes the construction of "[a] mammalian cell expression vector containing a fused sequence of nt 225 to nt 1650 encoding for a gag region and nt 5957 to n t8582 for an env region." Other examples

describing fusion protein expression systems include Example 3.5, which is titled "Expression of SOD-p31 fusion protein;" Example 3.6, which is titled "Expression of SOD-env5b fusion protein;" and Example 3.7, which is titled "Expression of β-gal-env fusion proteins." Again, none of these examples describe a plasmid with HCMV components.

Prosecution History of the '688 Patent

Novartis's predecessor in interest, Chiron Corporation ("Chiron"), filed the application for the '688 Patent on August 10, 1994. As noted above, the '688 Patent addressed the human immunodeficiency virus, or HIV, and the DNA that encodes HIV. The invention was directed to the use of those nucleotide sequences in diagnosis and treatment of HIV.

a. 1995 Amendments

In 1995, Chiron submitted amendments to the claims that added, for the first time, claims for a vector for expression of a polypeptide in a mammalian cell. Among other claims, these amendments added a claim reciting an isolated nucleic acid molecule comprising an HCMV IE1 enhanced promoter. This became Claim 17 following the addition in 2007 of the clause recited below.

As described more fully in the March 20 Opinion, the 1995 amendments relied solely on Example 2.3.2 and the associated Figure 29 as support for the new claims. Notably, in an April

1996 communication to the PTO, Chiron asserted that the description of the pCMV6a vector in Example 2.3.2 and Figure 29 was "sufficient to support all of applicants [sic] pending claims."

b. 2007 Amendments

In January 2007, after the PTO rejected 21 of the patent's claims in reexamination proceedings, Novartis submitted additional amendments to the '688 Patent. These amendments added the following underlined language to Claim 17:

> 17. An isolated nucleic acid molecule comprising an enhanced promoter, wherein the enhanced promoter comprises the human cytomegalovirus immediate early region HCMV IE1 promoter and the first intron proximate to the 3' end of the HCMV IE1 promoter and wherein the enhanced promoter is operably linked to a nucleic acid sequence encoding a mammalian polypeptide or a heterologous mammalian virus polypeptide.

In its remarks accompanying this amendment, Novartis explained that the specification provided support for this amendment through its discussions of mammalian virus polypeptides -- including gp120, the HIV protein discussed in Example 2.3.2 -- and mammalian polypeptides. It explained:

> Support for the amendments may be found throughout the specification. . . . The specification provides an example of expression of a mammalian virus polypeptide (gp120) using the claimed system in the specification from [Example 2.3.2]. In addition, the specification discusses other mammalian virus polypeptides and mammalian polypeptides to be expressed such as env . . . , tPA/gp160 (. . . -- a mammalian polypeptide fused to a mammalian viral polypeptide . . .), gag-env fusion . . . and various immunoglobulins from any

> mammalian source (. . . mammalian polypeptides). . . .

The PTO again rejected the amended claims, including Claim 17, on March 28, 2007.

c. Novartis's Arguments on Reexamination

In its communications with the PTO during the 2006-2009 reexamination of the '688 Patent, Novartis argued that amended Claim 17 should not be rejected. In particular, it engaged in argument regarding whether amended Claim 17 as well as its disclosure of "mammalian polypeptide" and "heterologous mammalian virus polypeptide" found adequate support in the specification.

In its November 2, 2007 brief in support of its appeal of the PTO's continued rejection of claims in the '688 Patent, Novartis pointed to Example 2.3.2 and Figure 29 as providing support for the entirety of its amended claims, including Claim 17. It described the claimed subject matter of the patent as "a non-human mammalian host cell expression system for improved expression of a polypeptide" and explained that "[s]uch an expression system is demonstrated in the specification on Col. 27, line 66 through Col. 28, line 3 [Example 2.3.2] and Figure 29." Novartis also stated that "[t]he claimed subject matter is also directed to an isolated nucleic acid molecule" and

explained that support for this molecule was also found in Example 2.3.2 and Figure 29.

In arguing that "mammalian polypeptide" and "mammalian virus polypeptide" found support in the specification, Novartis pointed to Example 2.3.2's description of expression of the HIV protein, gp120. It also explained that "[s]upport for 'a mammalian polypeptide or a heterologous mammalian virus polypeptide coding sequence' may be found, for example, [] in Examples 2.2.2 and 2.3.1 (demonstrating tissue plasminogen activator (a mammalian polypeptide) fused to gp160 or to gp120 (two heterologous mammalian viral polypeptides))."

On reexamination, Novartis emphasized the vector described in the claims -- rather than the protein to be expressed using that vector -- as the novel invention at issue in the claims. In a July 2007 communication with the PTO, it explained that the claimed invention relates to "a newly identified transcriptional regulatory region operably linked to a heterologous polypeptide, in preferred embodiments, a mammalian polypeptide or a mammalian virus polypeptide." In its reply brief dated March 7, 2008 in support of its appeal, it argued that "one of skill in the art would have no difficulty in understanding what a 'mammalian polypeptide or a heterologous mammalian virus polypeptide' is as neither concept is novel to this patent."

The PTO confirmed all 24 claims in the '688 Patent, as amended, on September 25, 2009. A reexamination certificate for the '688 Patent was issued on December 22, 2009.

The Disputed Terms

The parties dispute whether Claim 17 of the '688 Patent describes DNA technology that includes non-naturally occurring proteins (i.e. proteins engineered or fused through the combination of segments of naturally occurring proteins) or whether it contemplates only the use of proteins naturally found in mammals. This disagreement is of central importance to Novartis's infringement claim because aflibercept, the key ingredient in the accused products, is a fusion protein. The parties also disagree whether Claim 17 describes a technology focused on transcription. Finally, the parties disagree whether Claim 17's invention includes an enhancer region.

These three disagreements arise from their disputes over the construction of three separate terms in Claim 17. These terms also appear in other claims in the '688 Patent. The first disputed term, "mammalian polypeptide," also appears in Claim 13. The second disputed term, "operably linked" also appears in Claims 1, 4, 5, 9, 13, 15, 19, 20, 21, and 22. The third disputed term, "enhanced promoter," also appears in Claim 22.

Claim 17 and certain other claims in which the terms appear, with the disputed terms underlined, are set forth below.

1. A non-human mammalian host cell expression system for improved expression comprising a non-human mammalian host cell with a vector for expression of a polypeptide in a mammalian cell comprising a first polynucleotide sequence that comprises:
a) an upstream SV40 origin of replication;
b) a downstream SV40 polyadenylation region;
c) a transcription regulatory region from human cytomegalovirus immediate early region HCMV IE1, wherein the transcription regulatory region includes the first HCMV IE1 intron proximal to the 3' end of the HCMV IE1 promoter, is interposed between the SV40 origin of replication and the SV40 polyadenylation region, and is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the transcription regulatory region, and
d) the polypeptide coding sequence encoding a heterologous polypeptide operably linked downstream of the transcription regulatory region.

. . .

13. A vector produced by the process comprising linking together in an operative manner:
a) a SV40 origin of replication;
b) a SV40 polyadenylation region;
c) a transcription regulatory region from human cytomegalovirus immediate early region HCMV IE1, wherein said regulatory region includes the first HCMV IE1 intron proximal to the 3' end of the HCMV IE1 promoter and is capable of directing the transcription of a polypeptide coding sequence operably linked downstream therefrom; and
d) the polypeptide coding sequence encoding a mammalian polypeptide or a heterologous mammalian virus polypeptide operably linked downstream of the transcription regulatory region.

. . .

17. An isolated nucleic acid molecule comprising an enhanced promoter, wherein the enhanced promoter comprises the human cytomegalovirus immediate early region HCMV IE1 promoter and the first intron proximate to the 3' end of the HCMV IE1 promoter and wherein the enhanced promoter is operably linked to a

> nucleic acid sequence encoding a mammalian polypeptide or a heterologous mammalian virus polypeptide.
>
> . . .
>
> 22. A vector for expression of a polypeptide in a mammalian cell, comprising:
> a) an upstream origin of replication;
> b) a downstream polyadenylation region; and
> c) the nucleic acid molecule of claim 17 interposed between the origin of replication and the polyadenylation region, wherein the enhanced promoter region is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the promoter region.

Procedural History

Novartis filed this lawsuit on March 19, 2018. This lawsuit is brought over three years after the expiration of the '688 Patent and almost seven years after the accused Regeneron products first entered the market. On March 20, 2019, this Court issued the March 20 Opinion, construing five disputed terms. Fact discovery closed on March 29. On April 1, the parties stipulated to a judgment of non-infringement as to all but Claim 17. The parties exchanged opening expert reports on April 5 and reply expert reports on June 23. Expert discovery is set to close three weeks from today.

In a July 12 letter to the Court, Regeneron sought construction of the three additional terms at issue in this Opinion. Regeneron explained that the parties' dispute over the construction of these terms had come to light over the course of expert discovery. On July 15, the Court ordered briefing on

construction of the three additional terms. The briefing was fully submitted on July 31.

Discussion

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." Aventis Pharm. Inc. v. Amino Chems. Ltd., 715 F.3d 1363, 1373 (Fed. Cir. 2013) (citation omitted). "When the parties present a fundamental dispute regarding the scope of a claim term, it is the court's duty to resolve it." Eon Corp. IP Holdings v. Silver Spring Networks, 815 F.3d 1314, 1318 (Fed. Cir. 2016) (citation omitted).

In construing a patent claim, which is a question of law, courts "should look first to the intrinsic evidence of record, i.e., the patent itself, including the claims, the specification and, if in evidence, the prosecution history." Am. Calcar, Inc. v. Am. Honda Motor Co., Inc., 651 F.3d 1318, 1336 (Fed. Cir. 2011) (citation omitted). Courts, however, should not read meaning into claim language that is clear on its face. See Tate Access Floors, Inc. v. Interface Architectural Res., Inc., 279 F.3d 1357, 1371 (Fed. Cir. 2002). Claim construction is not a backdoor process by which the scope of a claim is narrowed or expanded. See Terlep v. Brinkmann Corp., 418 F.3d 1379, 1382 (Fed. Cir. 2005).

"In construing claims, district courts give claims their ordinary and customary meaning, which is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." Cont'l Circuits LLC v. Intel Corp., 915 F.3d 788, 796 (Fed. Cir. 2019) (citation omitted). The ordinary meaning of a claim term is its meaning "to the ordinary artisan after reading the entire patent." Aylus Networks, Inc. v. Apple Inc., 856 F.3d 1353, 1358 (Fed. Cir. 2017) (citation omitted). Thus, ordinary meaning is not something that is determined "in a vacuum." Eon Corp. IP Holdings, 815 F.3d at 1320 (citation omitted).

If a claim term does not have an ordinary meaning, and its meaning is not clear from a plain reading of the claim, courts turn in particular to the specification to assist in claim construction. Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc., 711 F.3d 1348, 1361 (Fed. Cir. 2013). Through the specification, a patentee "can act as his own lexicographer to specifically define terms of a claim contrary to their ordinary meaning." Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc., 467 F.3d 1370, 1376 (Fed. Cir. 2006) (citation omitted). But, "[t]o act as its own lexicographer, a patentee must clearly set forth a definition of the disputed claim term other than its plain and ordinary meaning." Cont'l Circuits LLC, 915 F.3d at 796 (citation omitted). "Usually,

[the specification] is dispositive; it is the single best guide to the meaning of a disputed term." Power Integrations, 711 F.3d at 1361 (citation omitted). Since the purpose of the specification is "to teach and enable those of skill in the art to make and use the invention," it often provides "an example of how to practice the invention." Phillips v. AWH Corp., 415 F.3d 1303, 1323 (Fed. Cir. 2005). But, while courts use the specification "to interpret the meaning of a claim," they must "avoid the danger of reading limitations from the specification into the claim" itself. Id. Although the specification often describes specific embodiments of the invention, the Federal Circuit has repeatedly warned against confining the claims to those embodiments. Id. Moreover, "[w]hile claims are to be interpreted in light of the specification, all that appears in the specification is not necessarily within the scope of the claims and thus entitled to protection." Novo Nordisk of N. Am., Inc. v. Genentech, Inc., 77 F.3d 1364, 1369 (Fed. Cir. 1996).

The prosecution history may "inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution." Phillips, 415 F.3d at 1317. Indeed, because the prosecution history includes the applicant's express representations made to the PTO examiner, it may be "of critical

significance in determining the meaning of the claims." Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996). "Any explanation, elaboration, or qualification presented by the inventor during patent examination is relevant" to claim construction. Fenner Investments, Ltd. v. Cellco P'ship, 778 F.3d 1320, 1323 (Fed. Cir. 2015). The prosecution history's instructive value is mitigated, however, by the fact that it "represents an ongoing negotiation between the PTO and the applicant ... [and] often lacks the clarity of the specification." Phillips, 415 F.3d at 1317.

A court may also consider extrinsic evidence, such as dictionaries and treatises, but such extrinsic evidence is "generally of less significance than the intrinsic record." Takeda Pharma. Co. Ltd. v. Zydus Pharma. USA, Inc., 743 F.3d 1359, 1363 (Fed. Cir. 2014). If the meaning of the claim is clear from the intrinsic evidence alone, resort to extrinsic evidence is improper. Boss Control, Inc. v. Bombardier Inc., 410 F.3d 1372, 1377 (Fed. Cir. 2005).

"[A] court may not use the accused product or process as a form of extrinsic evidence to supply limitations for patent claim language." Wilson Sporting Goods Co. v. Hillerich & Bradsby Co., 442 F.3d 1322, 1331 (Fed. Cir. 2006). This rule, however, "does not forbid awareness of the accused product or

process to supply the parameters and scope of the infringement analysis, including its claim construction component." Id.

Regeneron and Novartis each put forward conflicting constructions purportedly reflecting what they assert is the plain and ordinary meaning of the three disputed terms: "mammalian polypeptide," "operably linked," and "enhanced promoter." Each term is considered in turn.[4]

Before doing so, however it is useful to repeat Claim 17. It provides:

> 17. An isolated nucleic acid molecule comprising an enhanced promoter, wherein the enhanced promoter comprises the human cytomegalovirus immediate early region HCMV IE1 promoter and the first intron proximate to the 3' end of the HCMV IE1 promoter and wherein the enhanced promoter is operably linked to a nucleic acid sequence encoding a mammalian polypeptide or a heterologous mammalian virus polypeptide.

(Emphasis supplied).

Claim 17 generally describes a fragment of the vector or plasmid depicted in Figure 29. It describes a molecule comprising two components and their orientation to each other.

[4] Novartis also argues that because Regeneron failed to identify the three disputed terms at issue in this Opinion during the parties' initial claim construction process, it has waived any arguments regarding construction of additional terms. Not so. As described above, the claims at issue in this litigation have narrowed significantly since the initial claim construction period. Here, the parties present genuine disputes as to material terms in the sole remaining claim. The Court has a duty to resolve such disputes. See Eon Corp. IP Holdings, 815 F.3d at 1318.

It labels this molecule an enhanced promoter and explains that it is operably linked to a nucleic acid sequence that encodes one of two proteins: a mammalian polypeptide or a heterologous mammalian virus polypeptide. As described above, heterologous means from a different organism and, in the context of Claim 17, is understood to mean a mammalian virus polypeptide that is not from the HCMV virus.

I. "mammalian polypeptide"

Novartis proposes that the term "mammalian polypeptide" be construed to include fusion proteins. It proposes: "a precursor protein or a complete mature protein or fragment therof, including portions of, or entire polypeptides of, two or more different mature polypeptides, the sequence(s) for which are of mammalian origin." Regeneron proposes the following: "a polypeptide that is found naturally in a mammal." Regeneron is correct.

There is nothing in the claims, specification, or prosecution history to indicate that the term "mammalian polypeptide" should be afforded any meaning other than its commonly understood meaning, that is, a polypeptide that is found naturally in a mammal. Neither the term "mammalian polypeptide" nor the term "mammalian virus polypeptide" appear in the specification. This is unsurprising given that these terms were added to the claims for the first time in 2007 and

the specification, which dates from the 1987 filing of an antecedent patent, was never amended.

Example 2.3.2, the sole example in the specification that discloses the claimed invention, does not describe a mammalian polypeptide. It describes a vector for the expression of gp120, which is an HIV protein, that is, a mammalian virus polypeptide.

Moreover, when the specification discussed fusion proteins, which it did in passages other than Example 2.3.2, it did so by using the term "fusion protein." The term "fusion protein" is used to describe an engineered protein created by fusing portions of two different naturally occurring proteins together. Nowhere in the specification did the inventors use the terms mammalian polypeptide, or mammalian virus polypeptide, to refer to a fusion polypeptide. Thus, the inventors used the term "fusion protein" to describe man-made polypeptides and chose not to include such a term in Claim 17.

The prosecution history also indicates that the ordinary understanding of the term is the proper construction of the term "mammalian polypeptide." Novartis's defense of its claims following their amendment in 2007 focused on the invention of a vector and not on the protein to be expressed in the host cell through use of the vector. Indeed, Novartis disclaimed any special meaning for the term mammalian polypeptide. For example, Novartis asserted that the "claim element 'mammalian

polypeptide' . . . is not a novel element that has never been characterized." Through this statement, and others similar to it, Novartis assured the PTO that it was not importing any specific definition for the term or acting as a lexicographer.

In light of this uniform and uncomplicated record, the term "mammalian polypeptide" should be given its plain and ordinary meaning as understood by a person of ordinary skill in the art. The parties agree that dictionaries at the time the patent was filed define "mammalian" to mean "of relating to, or characteristic of mammals: belonging to the [class of] Mammalia." This definition most naturally suggests that the term is restricted to polypeptides that may be found naturally in a mammal. The complex, multi-faceted definition of the term "mammalian polypeptide" that Novartis suggests finds no support in the claims, the specification, or the prosecution history. Novartis has not shown, therefore, that one learned in the art would have understood the term as it proposes.

Novartis makes principally three arguments in support of its construction. It first relies on references in the specification to fusion proteins. These references do not appear in Example 2.3.2[5] or Figure 29 of the specification -- the

[5] Example 2.3.2 describes gp120, an HIV polypeptide, being inserted into a recombinant plasmid, which, when inserted into a host cell, directs higher levels of expression of gp120. While gp120 may be but one example of a polypeptide that could be used

only disclosure of the claimed invention in the specification -- and, as such, are of limited assistance when construing Claim 17's terms. Nor, as already explained, do these references use the term "mammalian polypeptide" to describe fused proteins. While one learned in the art would certainly understand that fused proteins were polypeptides, that is not the question at hand. The issue is how that skilled practitioner would understand the reference to "mammalian polypeptide" in Claim 17 and whether she would understand it to refer not only to proteins that naturally occur in mammals but also to scientifically engineered proteins that combine different kinds of mammalian DNA. The claim would have had to use different terminology to convey the meaning Novartis suggests.

In a related argument, Novartis emphasizes that during the reexamination of the '688 Patent, it relied on the specification's recital of fused proteins. During that process Novartis pointed to the specification's disclosure of the human tissue plasminogen activator (tPA) (a mammalian polypeptide) fused to an HIV, or viral, polypeptide as examples of the fact

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in the invention, nowhere does this example suggest that expression of a man-made or fusion polypeptide was part of the invention disclosed in that example. In contrast, other examples that describe the expression of specific "fusion proteins" do so through methods that do not use the claimed expression system in Example 2.3.2 and the '688 Patent's claims, that is an expression system using Figure 29's vector and HCMV.

that either a mammalian polypeptide or mammalian virus polypeptide could be expressed. It emphasizes that it relied on these disclosures to support the addition of the term "mammalian polypeptide" during reexamination. The parties debate whether the examples to which Novartis points indeed describe a "fusion protein." Regardless, the examples in which tPA is described as fused to a mammalian viral polypeptide do not support the '688 Patent's claims. The examples in which this feature is discussed -- examples 2.2.2 and 2.3.1 -- make no mention of HCMV, while regulatory components derived from the HCMV virus are central to Claim 17, and to all of the other claims in the '688 Patent. In any event, the fact that Novartis referred to the fused proteins during the prosecution history does not overcome the principal hurdle it faces in presenting its preferred construction of the term "mammalian polypeptide": when Novartis wanted to refer to fused proteins it described them as fused proteins and not as mammalian polypeptides.[6]

[6] In its reply, Novartis contends for the first time that if Regeneron's proposed construction were to be applied consistently to the '688 Patent's terms, "mammalian cells" and "mammalian host cells" (terms used throughout the specification and claims) would exclude the engineered COS and CHO cell lines used commonly in the biotechnology industry (COS cells are monkey kidney cells. CHO cells are Chinese hamster ovary cells.) Arguments presented for the first time in reply will not be considered. Patterson v. Balsamico, 440 F.3d 104, 113 n.5 (2d Cir. 2006).

Finally, Novartis argues that Regeneron's proposed construction -- "a polypeptide found naturally in a mammal" -- lacks adequate specificity. It argues that this definition could encompass a bacterial or viral protein because such proteins could be found naturally in a mammal although they do not originate from the mammalian genome. Claim 17 describes "a nucleic acid sequence encoding a mammalian polypeptide or a heterologous mammalian virus polypeptide." A skilled artisan would have understood that "mammalian polypeptide" did not encompass "mammalian virus polypeptides" but rather was intended to describe a polypeptide naturally produced by and found in mammals. In other words, a polypeptide of the mammalian genome that is found in nature. The expansive reading of "found naturally in a mammal" that Novartis cautions against is illogical in the context of the entire claim.

The '688 Patent does not use the term "mammalian polypeptide" to describe a man-made polypeptide of mammalian genetic origin. The term "mammalian polypeptide" is construed as "a polypeptide that is found naturally in a mammal."

II. "operably linked"

Novartis proposes that the term "operably linked" be construed as "arranged so that the polypeptide is expressed." Regeneron proposes: "arranged in a functional manner, where the enhanced promoter must be arranged with respect to the nucleic

acid sequence encoding the polypeptide so as to direct its transcription in the host cell." The term operably linked refers to functionality.[7] Read in the context of Claim 17, the functionality being referred to is transcription. Therefore, Regeneron's construction is correct.

The term "operably linked" appears in six claims in addition to Claim 17. It is used to describe the relationship between a regulatory DNA sequence, including a promoter, and the sequence of nucleotides that code for the protein of interest. Claim 17 describes a molecule "comprising an enhanced promoter . . . wherein the enhanced promoter is operably linked to a nucleic acid sequence encoding" one of two polypeptides. Claim 22 incorporates the reference to the nucleic acid sequence of Claim 17. It claims in relevant part: a "vector for expression of a polypeptide in a mammalian cell, comprising" three components. The third component is "the nucleic acid molecule of claim 17 . . . wherein the enhanced promoter region is

[7] The March 20 Opinion discusses the term "operably linked" in the context of construing the term "SV40 origin of replication." There, the Court found that the claims' use of "operably linked" indicated that the element -- in that case the SV40 origin of replication -- was functional in the host cell. Expression of the protein of interest was improved through incorporation of an SV40 origin of replication. See March 20 Opinion, 2019 WL 1274790, at *12. As a result, the March 20 Opinion rejected Novartis's proposed construction which would have contemplated an SV40 origin of replication that would be non-functional in certain host cells. Id. at *13. The instant construction of "operably linked" is consistent with that finding.

capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the promoter region." Claims 1, 4, 5, 9, and 13 all describe vectors. They describe one of the elements of the claimed vector as

> a transcription regulatory region from human cytomegalovirus immediate early region HCMV IE1 wherein the transcription regulatory region . . . is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the transcription regulatory region.

(Emphasis supplied.)

The term "operably linked" does not appear in the specification. This includes Example 2.3.2, which is the only example in the specification that discloses the patented claims.

The parties agree that, in the context of Claim 17, an "operably linked" enhanced promoter is one that is arranged with respect to the nucleic acid sequence encoding a polypeptide in such a manner that "it directs the transcription of that nucleic acid sequence once in the host cell." As explained above, transcription refers to the process wherein DNA coding for a polypeptide is copied onto a template within the cell into which the vector has been inserted. This agreement should end the matter. Novartis, however, contends that this construction is incomplete and too broad because it does not require that the promoter transcribe the gene encoding the polypeptide in such a way that the transcribed sequence will be translated into the

polypeptide it codes for, that is, read by cellular machinery in the host cell to produce the protein. In other words, Novartis contends that "operably linked" must be construed to require not just copying but also expression of the polypeptide.

Novartis's construction adds a limitation not found in the claims. A person of ordinary skill in the art would understand that a promoter is a region of regulatory DNA that directs transcription. It does not direct translation. Similarly, an "enhanced promoter" refers to enhanced transcription; it does not refer to translation. As such, Claim 17's description of an enhanced promoter that is "operably linked" to a gene describes an enhanced promoter that functions to direct transcription of that gene.

This construction is underscored by the reading of the other claims that associate the term "operably linked" with either an enhanced promoter or a transcription regulatory region. In each case, the claims refer explicitly to transcription in describing the linkage between the regulatory region and the gene encoding a polypeptide to which it is "operably linked."

Novartis contends that because the claims of the '688 Patent describe an expression system, "operably linked" in Claim 17 must mean "resulting in expression." Novartis is correct that many of the claims of the '688 Patent are directed to a

vector for expression of a protein in a host cell. While that overall focus of the patent must be kept in mind, that focus may not inject meaning into components of the claims that cannot properly be found there. The construction of a claim and its components should be consistent with the purpose of the invention, but that purpose may not distort the meaning of the individual claim terms.

Construing Claim 17 as necessarily resulting in expression would impermissibly import elements not described in that claim and would run counter to the commonly understood function of a promoter.[8] The invention described in Claim 17 is not an expression system. Where the patentees sought to describe an expression system in a claim, they unambiguously did so. Instead, Claim 17 describes a sub-component of a vector. This is made explicit in Claim 19, which describes Claim 17 as one of three components of a vector. Claim 19 recites a "vector for expression of a polypeptide in a mammalian cell, comprising the nucleic acid molecule of [C]laim[] 17, wherein the nucleic acid

[8] Novartis also points to the '688 Patent's prosecution history for support for the contention that "operably linked" necessarily means resulting in expression. The passages to which it cites are inapposite. While they demonstrate that an "operably linked" cellular component may sometimes result in increased expression of a gene, these passages do not provide guidance on how this term should be construed in the context of Claim 17.

molecule is capable of directing the transcription of a polypeptide coding sequence operably linked downstream of the nucleic acid molecule."[9] While the enhanced transcription described in Claim 17 furthers the '688 Patent's goal of improving expression, it describes only a necessary step in the ultimate expression of the protein in a host cell.

Novartis's proposed construction would improperly import limitations to Claim 17.[10] Accordingly "operably linked" in the context of Claim 17 is construed as "arranged in a functional manner, where the enhanced promoter must be arranged with respect to the nucleic acid sequence encoding the polypeptide so as to direct its transcription in the host cell."

III. "enhanced promoter"

Novartis contends that the term "enhanced promoter" should be construed as "a promoter comprising the hCMV IE1 promoter and the first intron proximate to the 3' end of the hCMV IE1 promoter." Regeneron argues that "enhanced promoter" should be

[9] "In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.'" CIAS, Inc. v. All. Gaming Corp., 504 F.3d 1356, 1360 (Fed. Cir. 2007).

[10] Novartis in its reply speculates that Regeneron's proposed construction could lead to partial transcription that would be incompatible with protein expression. Novartis points to nothing in the claims, specification, or prosecution history, however, to indicate that a concern with that problem requires the term "operably linked" to be read more narrowly in Claim 17 than would otherwise be the case.

construed as: "the promoter region of hCMV IE1 having hCMV IE1 enhancer, promoter, and first intron sequences." While Regeneron's construction adds an HCMV IE1 enhancer, Novartis's construction is lifted from Claim 17 itself.

The term "enhanced promoter" appears in Claims 17 and 22. Claim 17 describes "an enhanced promoter, wherein the enhanced promoter comprises the human cytomegalovirus immediate early region HCMV IE1 promoter and the first intron proximate to the 3' end of the HCMV IE1 promoter." Claim 22 describes a vector for expression that includes as one of its components the nucleic acid molecule of claim 17 "wherein the enhanced promoter region is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the promoter region."

The term "enhanced promoter" does not appear in the specification. Figure 29, which is the sole embodiment of the claimed invention, describes a vector. It depicts the section of the vector described in Claim 17 using the labels "HCMV IE1 enh/pro" and "HCMV intron."

As already noted, Novartis argues that "enhanced promoter" should be construed using the definitional language employed in Claim 17. After all, a court should "presume that the terms in the claim mean what they say." Power Integrations, Inc., 711 F.3d at 1360. Critical to this construction, however, is Claim

17's use of the term "comprising," which the parties agree means "including." "Comprising" does not create an exclusive list. CIAS, Inc. v. All. Gaming Corp., 504 F.3d 1356, 1360 (Fed. Cir. 2007).

Regeneron contends that the '688 Patent's claims and specification, when read together, identify a fragment of the vector as including the enhancer, promoter, and first intron sequence of HCMV IE1. It contends that that same sequence is variously described as the "enhanced promoter," "promoter region," and "transcription regulatory region." That sequence, as explained in Example 2.3.2 is a 1.7 kbp fragment.[11] Regeneron argues that Novartis's construction, which eliminates the need to include the enhancer segment from the fragment, is also at odds with the prosecution history. In a 1996 rejection of the '688 Patent application, the PTO explained that one of skill in the art would recognize the "transcription regulatory region" "as being the 1.7 kbp SspI-SalI set forth in the specification."

[11] Kbp, or kilo base pair, is a term used to described the length of a DNA or RNA molecule. Example 2.3.2 states: "Plasmid pCMV6a is a mammalian cell expression vector which contains the transcription regulatory region from human cytomegalovirus immediate early region." It goes on to explain that this "plasmid contains . . . the HCMV IE1 promoter as a 1.7 kbp Sspl-SalI fragment derived from a subclone of the human cytomegalovirus." Example 2.3.2 then states: "[t]he HCMV IEl promoter region contains the region encoding the first exon (5' untranslated), the first intron and the start of the second exon."

Novartis takes the position that the term "enhanced promoter" should be understood as comprising solely the identified promoter and first intron regions. But, unless the first intron itself can be understood to create an "enhanced promoter" when combined with a promoter, this construction fails to recognize the term "enhanced." Novartis points to nothing in the specification or prosecution history to support such a construction.

Alternatively, Novartis argues that if an enhancer must be added to the promoter and first intron sequences to create an "enhanced promoter," it need not encompass the entire 1.7 kbp SspI-SalI fragment described in Example 2.3.2. Rather, Novartis identifies a "complex enhancer" described in prior art as extending about 480 base pairs (a much smaller distance than 1.7 kbp) upstream of the HCMV IE1 promoter.

A claim construction hearing will be necessary to resolve this dispute. To give effect to the adjective "enhanced" it will be necessary to better understand the science at issue as that science was understood by one skilled in the art at the time of the invention. The primary question to be addressed is: Would one skilled in the art understand the first intron to "enhance" the promoter or would "enhanced" be understood to refer to something else?

For the reasons already explained, the specification is of limited assistance in the claim construction. While the able experts for the parties have been of great assistance in their written submissions, greater explication of the science at issue is necessary to resolve their final dispute.

Conclusion

Two of the disputed terms, as set forth in the parties' claim construction submissions, are construed as set forth above. An order will schedule a hearing to resolve the third dispute.

SO ORDERED:

Dated: New York, New York
August 14, 2019

DENISE COTE
United States District Judge